ORIGINAL ARTICLE

[Translated article] Epidemiology and Geographic Distribution of Generalized Pustular Psoriasis in Spain: A National Population-Based Study of Hospital Admissions from 2016 to 2020

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Abstract
Introduction: Little has been published on the epidemiology of generalized pustular psoriasis (GPP). The aim of this study was to describe and analyze the geographic distribution of hospital admissions for GPP in Spain.
Methods: We performed a cross-sectional study using the hospital discharge database of the Spanish Basic Minimum Data Set (CMBD), which is a mandatory data set of all admissions to public hospitals in the country. We included patients with a primary diagnosis of psoriasis or GPP at discharge for the period 2016–2020. We performed a descriptive analysis of clinical and sociodemographic characteristics of patients admitted with GPP, a spatial analysis at the province level assessing the presence of geographic heterogeneity and a GPP disease map.
Results: We detected 949 diagnoses of psoriasis and 744 primary diagnoses of GPP. Mean age of patients admitted with GPP was 62.2 years. Intensive care unit admissions were ordered for 6.1% of patients and 4.8% died. The overall incidence rate of newly hospitalized GPP patients during the study period was 3.18 cases per 1,000,000 person-years. The geographic distribution varied widely, with higher rates observed in the north-west of the country.
Conclusions: We describe the characteristics of GPP hospitalized patients in Spain and provide the first disease map for the country. The findings could help guide future research and suggest the possibility of genetic or environmental factors driving geographic differences.
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Epidemiología y distribución espacial de la psoriasis pustulosa generalizada en España: un análisis poblacional a nivel nacional basado en datos de ingresos hospitalarios (2016-2020)

Resumen

Introducción: Existen datos epidemiológicos escasos sobre la psoriasis pustulosa generalizada (PPG). El objetivo de este estudio fue describir los casos hospitalizados de PPG en España y evaluar su distribución espacial en el país.

Métodos: Se realizó un estudio transversal utilizando la base de datos de altas hospitalarias del conjunto mínimo básico de datos (CMBD) del Servicio Nacional de Salud. Se incluyeron los pacientes con un diagnóstico principal de psoriasis o un diagnóstico de PPG al alta hospitalaria entre 2016 y 2020. Se realizaron un análisis descriptivo de las características clínicas y sociodemográficas de los pacientes ingresados con PPG y un análisis espacial a nivel provincial, evaluando la presencia de heterogeneidad geográfica y elaborando mapas de enfermedad.

Resultados: Se identificaron 744 pacientes con un diagnóstico de PPG y 949 casos de otras formas de psoriasis como diagnóstico principal. Los hospitalizados con PPG tenían una edad media de 62,2 años. La proporción de ingresos en la Unidad de Cuidados Intensivos fue de 6,1% y la mortalidad de 4,8%. La tasa de incidencia global de PPG en el periodo de estudio fue de 3,18 casos nuevos hospitalizados por 1.000.000 de personas-año. La distribución espacial de las hospitalizaciones por PPG en España fue heterogénea, con mayores tasas en la región noroeste del país.

Conclusiones: Describimos las características de los pacientes hospitalizados con PPG en España y proporcionamos la primera aproximación cartográfica de la enfermedad en todo el país. Estos datos podrían ayudar a optimizar futuras investigaciones sobre esta enfermedad y apoyan la existencia de factores de riesgo genéticos o ambientales con una distribución geográfica desigual.

Introduction

Generalized pustular psoriasis (GPP) is a type of psoriasis characterized by an acute onset of multiple sterile pustules and generalized erythema with severe systemic symptoms.[1,2] It is an uncommon, life-threatening disease that frequently requires admission to hospital.[3]

GPP differs from other types of psoriasis.[4] Three genes have been linked to this disease, including the gene coding for the interleukin-36 receptor antagonist, a caspase recruitment domain family member 14 and the adaptor protein complex 1 subunit sigma 3.[5] However, they account for less than 30% of PPG cases, so the genetic variant in most patients remains unknown. The interleukin most closely related to PPG is IL-36 and new biologics directed against it are being developed for its treatment.[6] Notwithstanding, disease course is unpredictable, and scarce knowledge of its etiology and pathogenesis and of its epidemiology make it difficult to conduct randomized clinical trials and to develop an evidence-based treatment algorithm.[7]

Therefore, the objectives of the present study were to describe the epidemiologic characteristics of GPP in Spain, describe patients hospitalized with GPP, and evaluate the geographic distribution of the disease.

Material and Methods

We performed a cross-sectional study that collected administrative data from the Specialized Care Activity Registry, which provides information on hospital discharges from the Spanish Basic Minimum Data Set (CMBD) of the National Health Service. The CMBD is a database created by the Spanish Ministry of Health containing a series of data collected from discharge records of hospitals belonging to the Spanish National Health System, namely, the diagnostic code based on the *International Classification of Diseases (ICD), Tenth Revision (ICD-10)* and basic administrative, sociodemographic, and clinical information. The CMBD is a uniform data source that makes it possible to evaluate processes requiring admission to hospital and has been widely used for research purposes.[8–11]

Our study included patients diagnosed with GPP at discharge or with a primary diagnosis of other types of psoriasis (Table S1). We excluded patients with a primary diagnosis of psoriatic arthritis. The variables included were year of discharge, province, sex, age, place of residence, primary diagnosis or secondary diagnosis, department where the patient was treated during admission, need for intensive care, type of discharge (home, transfer to another hospital, or death), and readmission.

In the descriptive analysis, qualitative variables were expressed as absolute (relative) frequency distributions, and continuous variables were expressed as mean (SD). The χ^2 test was used to compare categorical variables and the *t* test to compare continuous data. The Cochran−Armitage test was used to evaluate trends toward hospitalization for GPP. Statistical significance was set at $P < .05$ (2-tailed). The statistical analysis was performed with Stata 17.[12]

Crude incidence rates of hospitalizations for GPP between 2016 and 2020 were calculated by adding the

Table 1 Epidemiological Data Comparing Hospitalization For Generalized Pustular Psoriasis With Other Types of Psoriasis.[a]

	Hospitalizations with generalized pustular psoriasis (n = 744)	Hospitalizations with other types of psoriasis (n = 949)	P[b]
Sociodemographic characteristics			
Age, y	62.2 (20.5)	58 (19.2)	<.001
Female sex, %	382 (51.3)	370 (39)	<.001
Clinical characteristics			
Admission to the dermatology department, %	121 (16.3)	407 (42.9)	<.001
Admission to the ICU, %	45 (6.1)	13 (1.4)	<.001
Mortality	36 (4.8)	14 (1.5)	<.001
Readmission, %	173 (23.3)	152 (16)	<.001

Abbreviation: ICU, intensive care unit.

[a] Continuous data are expressed as mean (SD); categorical data are expressed as absolute (relative) frequencies.

[b] P value after application of the *t* test to compare continuous variables and the χ^2 test or Fisher exact test, as applicable, to compare categorical data.

total case count for the period and dividing the result by the Spanish population at mid-2018 (data publicly available from the Spanish National Statistics Institute[13]) to obtain the estimated number of hospitalizations per 1,000,000 person-years for the country and for each province. Patients requiring readmission were only counted once.

The geographic analysis of GPP was performed by taking the province as the spatial unit. Spain is divided into 50 provinces, and as GPP is an uncommon disease, we expected small counts for many spatial units. The geographic distribution of the disease was assessed using empirical Bayes smoothing in order to take account of variance instability in areas with small counts. We prepared box maps to identify possible atypical values with a hinge value of 3, that is, those with rates lower than the 25th percentile minus 3 times the interquartile range (IQR), and rates greater than the 75th percentile plus 3 times the IQR. In order to determine whether the distribution of cases throughout Spain could be explained by chance or whether there was evidence of a spatial structure in the data, we analyzed the presence of global spatial autocorrelation using the Moran I for crude incidence data. To do so, we created a matrix with first-order contiguity-based spatial weights, where provinces sharing borders or corners were considered neighbors (Queen contiguity). The statistical findings were evaluated using pseudo *P* values based on permutation procedures in GeoDa, with 999 permutations.

Results

A total of 744 hospitalizations for GPP were recorded in Spain between 2016 and 2020, and there were 949 cases with a primary diagnosis of other types of psoriasis. Table 1 shows the characteristics of hospitalizations with GPP. Mean (SD) age at admission was 62.2 (20.5) years, with an even distribution between the sexes. The dermatology department managed 16.3% of GPP cases. In 6.1% of cases, the patient was admitted to the intensive care unit (ICU); 4.8% of patients died. Readmissions accounted for 23.3% of all hospitalizations.

Compared with other types of psoriasis (Table 1), patients with GPP were older (62.2 vs. 58.6 years, *P* < .001) and more frequently women (51.3% vs. 39.0%, *P* < .001). As for the department where the admission was managed, patients with GPP were less frequently admitted to dermatology if the primary diagnosis was another type of psoriasis (16.3% vs 42.9%, *P* < .001). Higher percentages were recorded for patients with GPP in terms of admission to the ICU (6.1% vs. 1.4%), readmission (23.3% vs. 16.0%), and death (6.1% vs. 1.4%) (*P* < .001). An increasing linear trend was observed in the percentage of admissions with GPP during the study period: 31.1% in 2016 vs. 58.8% in 2020 (*P* < .001).

The global incidence rate of new hospitalizations with GPP during the study period was 3.18 cases per 1,000,000 person-years. The incidence of GPP by province in Spain is shown in Fig. 1A, where we can see high values in the northwest and center of the country and in the southern province of Sevilla. A higher-risk area was identified in the northwest, especially in the provinces of Pontevedra and A Coruña (Fig. 1B). Findings support spatial heterogeneity in the distribution of cases throughout Spain. Global Moran's I indicated positive clustering with crude incidence rates with crude incidence rates (*I* = 0.20, pseudo *P* value = .012), indicating that cases were more geographically clustered than expected by chance and that incidence rates in the neighboring provinces tended to be more similar than in distant provinces.

Discussion

A total of 744 hospitalizations for GPP were recorded in Spain between 2016 and 2020, that is, 43% of all hospitalizations for psoriasis. Frequency of admission to the ICU and mortality were greater in cases of GPP than in other types of psoriasis. The global incidence rate was low and the distribution by province heterogenous, with the highest incidence recorded in the northwest.

This is the first study to provide national epidemiological data on hospitalization for GPP in Spain. Given that GPP is
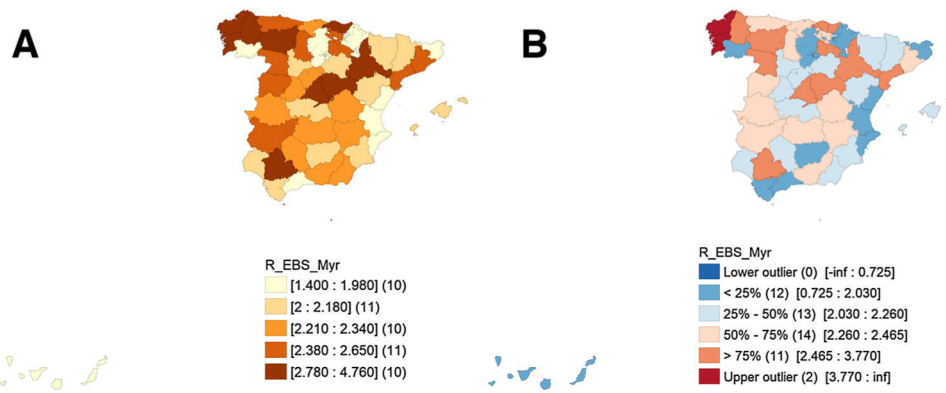
Figure 1   (A) Choropleth map showing the frequency of patients with generalized pustular psoriasis (GPP) admitted to hospital per 1,000,000 person-years between 2016 and 2020 in Spain. (B) Choropleth map (box map) showing the geographic distribution of patients admitted with GPP in Spain and highlighting atypical values (2016–2020). Note: Box map with a hinge value of 3. This identifies atypical low values (lower outlier) and values with rates lower than the 25th percentile minus 3 times the interquartile range (IQR) and atypical high values (upper outlier) as those with rates higher than the 75th percentile plus 3 times the IQR. The maps were created using GeoDa software.

a serious disease, it is expected that most patients will be hospitalized; therefore, our findings seem representative of the incidence of GPP in Spain. However, our study is subject to limitations, since the variables were collected from the CMBD. Information for this database is obtained from hospital discharge reports and could contain errors. Furthermore, it only collects information on patients admitted to hospital, thus entailing a potential selection bias due to differences in admission criteria according to the autonomous community. The comparison with other types of psoriasis could also be biased: since while it is likely most patients with GPP were admitted to hospital, it is unlikely that those diagnosed with psoriasis are representative of the psoriasis population in general.

Our study corroborates the low incidence of GPP, in line with publications from other countries. The incidence we recorded (3.18 patients hospitalized per million per year) was higher than in another White population (France, 0.64 cases per million per year).[14] Consistent with previous reports, GPP was more common in women,[7] whereas the mean age of participants was 10 years greater than in previous reports.[14]

In addition, we found that GPP is a serious disease, since the need for admission to the ICU and mortality were greater than in other types of psoriasis for which patients were hospitalized. Values for these markers of disease severity were higher than those reported by Hanna et al.,[15] who found that among 71 patients hospitalized with GPP, 0.04% were admitted to the ICU and 0.03% died. Readmissions accounted for 23% of hospitalizations, although there was no comparison with other studies. The authors also observed a progressive increase in the percentage of hospitalizations for GPP (31.1% of all hospitalizations for psoriasis in 2016 vs. 58.8% in 2020, $P < .001$), possibly because of a greater number of hospitalizations for GPP or a lower number of hospitalizations for other types of psoriasis.

Our study shows that the spatial distribution of GPP was heterogeneous throughout the country, with higher rates in the northwest. The prevalence of GPP varies throughout the world, and nationwide studies have been performed,[14,16] but

we were unable to find spatial studies assessing the incidence of GPP at the small area level.[17,18] Knowing how GPP affects different regions could form the basis for future studies evaluating the role of genetic and/or environmental risk factors in the development of GPP.

In conclusion, we report the incidence and characteristics of admissions for GPP in Spain and provide an estimate of the geographic distribution of the disease throughout the country. Out data could help to optimize future research on this disease, thus reinforcing the potential presence of genetic and environmental risk factors with an uneven geographic distribution.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Acknowledgments

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ad.2022.09.020.

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